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ELECTROPHYSIOLOGIC STUDIES

Increased Dispersion of "Refractoriness" in Patients With Idiopathic Paroxysmal Atrial Fibrillation

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The average interval between local depolarizations during atrial fibrillation, the so-called atrial fibrillation interval, was used as an index for local "refractoriness." This was based on the assumption that during fibrillation, cells are reexcited as soon as their refractory period ends. A very good correlation was found between refractory periods determined with the extrastimulus technique at a basic cycle length of 400 ms and atrial fibrillation intervals measured at the same epicardial sites of the right atrium.

This new technique was used to assess dispersion in atrial fibrillation intervals in 10 patients with idiopathic paroxysmal atrial fibrillation and in a control group of 6 patients who were undergoing cardiac surgery. After a routine median sternotomy a multiterminal grid with up to 40 electrodes was placed over the right atrium, and atrial fibrillation was induced by premature stimulation. The average fibrillation interval in the test group, recorded at 247 sites, was 152 ± 3 ms and that in the control group, recorded at 118 sites, was 176 ± 8.1 ms ($p < 0.05$). Dispersion in atrial fibrillation intervals, defined as the variance of the fibrillation intervals at all the recording sites, was three times larger in the group with paroxysmal atrial fibrillation than in the control group.

This study suggests that both a shorter refractory period and a larger dispersion in refractoriness are responsible for the recurrence of atrial fibrillation.

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Experimental animal studies (1,2) have shown that atrial fibrillation is based on multiple wavelet reentry. During this arrhythmia, many independent wavelets propagate in an ever-changing pattern around continuously shifting areas of conduction block (1,2). Dispersion in refractoriness is considered to favor the induction and maintenance of reentrant arrhythmias (3,4). Classic methods to determine refractory periods at many different sites are very time-consuming. Lammers et al. (5) used the average interval between local activations during atrial fibrillation as an index for local refractoriness. This procedure is based on the assumption that during fibrillation, cells are reexcited as soon as their refractory period ends. Recording of local atrial electrograms simultaneously at multiple sites during atrial fibrillation allows the assessment of spatial dispersion in atrial fibrillation intervals in a very short time.

We therefore measured atrial fibrillation intervals at multiple sites in the right atrium with the aim of determining spatial dispersion in "refractoriness" in patients with paroxysmal atrial fibrillation and in a control group of patients during cardiac surgery. The results of this study show that atrial refractoriness is shorter and spatial dispersion much greater in patients with paroxysmal atrial fibrillation than in control patients.

Methods

Study group. The study group consisted of a test and a control group of patients admitted to the hospital for antiarrhythmia surgery. The test group consisted of eight patients with drug-refractory idiopathic paroxysmal atrial fibrillation who underwent the "corridor" operation (6) and two patients operated on for symptomatic circus movement tachycardias due to the Wolff-Parkinson-White syndrome in association with paroxysmal atrial fibrillation. The six patients in the control group underwent surgery for symptomatic postinfarction ventricular tachycardia refractory to medical therapy. A detailed clinical and physical examination was obtained from each patient. All antiarrhythmic drugs were discontinued at least five drug half-lives before surgery. All patients underwent 24-h Holter monitoring and exercise electrocardiography for rhythm evaluation. In addition, the patients underwent hemodynamic and angiographic cardiac catheterization according to standard techniques. Both groups had normal atrial dimensions and

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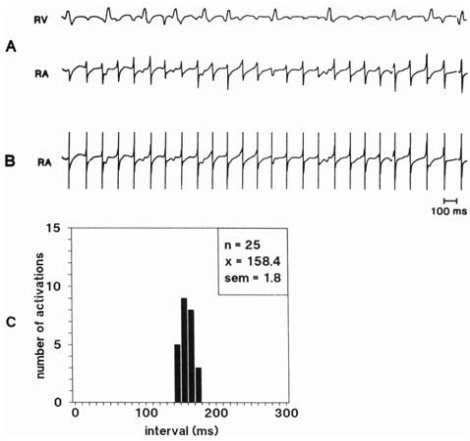

Figure 1. A, Electrograms during a 4-s period of atrial fibrillation recorded from an epicardial site on the right ventricle (RV) and a site on the right atrium (RA). B, Same tracing as the right atrial recording in A; the vertical lines are the activation moments as determined by an interactive computer program. C, Twenty-five intervals between activation moments are expressed in a histogram. The mean atrial fibrillation interval at this particular site (that is, the index of local refractoriness) was 158.4 ms.

atrioventricular valve function as judged by two-dimensional Doppler echocardiography.

The diagnosis of atrial fibrillation was made when 1) visible P waves on all 12 leads of the electrocardiogram (ECG) were absent, and 2) an irregular random ventricular response was present (7). Atrial fibrillation was considered paroxysmal if the fibrillatory process ended spontaneously after some seconds, minutes, hours or days (8). Atrial fibrillation was defined as idiopathic when it occurred without detectable heart disease (9). All patients gave informed consent to the study protocol.

Epicardial signal acquisition. A multiterminal grid electrode was used for simultaneous recording of epicardial electrograms. The grid electrode consisted of rectangular sheets of silicone rubber on which terminals (stainless steel hemispheres, 2-mm diameter) were fixed and arranged in a square lattice of either six columns and five rows or eight columns and five rows. The interelectrode distance was 7 mm. Recordings were made in the unipolar mode, with the signal of a needle in the left shoulder as reference.

Before acquisition, two hook electrodes were attached to the right atrium. One of these electrodes delivered an atrial reference signal. The other electrode was used as a stimulus electrode to induce atrial fibrillation in patients in the control group. During atrial fibrillation, the grid electrode was placed over the epicardial surface of the right atrium. Electrograms from all sites were recorded during two consecutive periods of 4 s and stored on disk. All recordings were made during normothermia with the heart closed.

Epicardial electrograms were filtered (low cutoff 1 Hz, high cutoff 1 kHz) and amplified (×200) together with surface ECG leads I, II and III and the atrial reference signal. Subsequently, these signals were fed into an LSI 112-based computer system by means of an 80-channel multiplexing analog to digital converter. Samples were taken every 4 ms. Ten epicardial signals, the surface leads, the atrial reference signal and a stimulation marker were continuously registered on a 16-channel recorder. For identifying the registrations stored by the computer, a registration code was sent to the on-line chart recorder each time a registration was frozen. With each registration, a 4-s period of fibrillation was stored. Data were transmitted to and stored in a PDP-11/73 computer for analysis.

Signal analysis. An interactive computer program indicated local activation times in each electrogram. The intrinsic deflection of the unipolar electrogram, indicating local activation during atrial fibrillation, was arbitrarily defined as a negative deflection with a steepness of ≥0.5 V/s over a ≥4-ms period. Figure 1 shows an example of a 4-s period of atrial fibrillation recorded at one site. The vertical lines are activation moments as detected by the computer. Subsequently, histograms of the intervals between local activations were made. The atrial fibrillation interval was defined as the mean of the histogram.

Validation of the method. In a previous study (10), a very good correlation was found between local refractory periods and local ventricular fibrillation intervals in the canine heart. Moreover, transmembrane potentials recorded from the fibrillating ventricle showed an absence of a diastolic interval between successive action potentials, supporting the as-

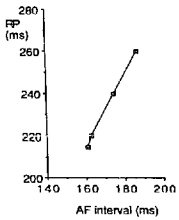

Figure 2. Relation between atrial fibrillation (AF) intervals and the refractory period (RP) determined with the extrastimulus technique at four epicardial sites. The basic cycle length was 400 ms during determination of the refractory period.

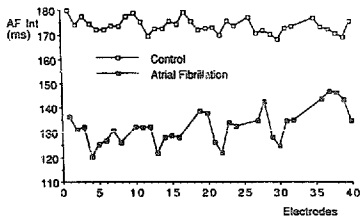

Figure 3. Atrial fibrillation intervals (AF Int) recorded simultaneously at 37 sites (Electrodes) in a control patient and at 32 sites in a patient with paroxysmal atrial fibrillation.

sumption that during fibrillation cells are reexcited as soon as they recover their excitability (10). In two patients undergoing antiarrhythmic surgery, we measured refractory periods at four epicardial sites on the right atrium, using the extrastimulus technique. The atrium was paced from each electrode site at a basic cycle length of 400 ms. After eight basic cycles, a premature stimulus of twice diastolic threshold was applied with a pulse duration of 2 ms. The shortest coupling interval of the premature pulse resulting in a propagated response was taken as the effective refractory period at that site. Subsequently, atrial fibrillation was induced by premature stimulation and fibrillation intervals recorded from the same sites as described for epicardial signal acquisition.

Data analysis. Data were analyzed with the use of the Student *t* test and the F test. Dispersion in refractoriness was determined by calculating the variance (squared standard deviation) of the mean atrial fibrillation interval at all sites. The spatial dispersion in the test group was compared with that in the control group by dividing the variance in both groups. This ratio was considered significant if it exceeded the appropriate F value.

Results

Atrial fibrillation interval. Figure 1A shows a right ventricular and right atrial electrogram of a 4-s period of atrial fibrillation in a patient. Figure 1B shows the same right atrial signal including the activation moments as determined with the use of an interactive computer program (see Methods). From the corresponding histogram, the mean atrial fibrillation interval of 158.4 ms (Fig. 1C) at this particular site was calculated. This procedure was performed at all recording sites.

Figure 2 shows a plot of atrial fibrillation intervals and refractory periods determined at four different atrial sites at a basic cycle length of 400 ms in one patient. There was a very good correlation between both measurements.

Atrial fibrillation versus control. Figure 3 shows atrial fibrillation intervals measured simultaneously at multiple sites in a control patient and in a patient with paroxysmal atrial fibrillation. The mean atrial fibrillation interval in the control patient was 173 ± 2.4 ms and in the other patient 132 ± 7.3 ms. The spatial distribution of differences in atrial fibrillation intervals at all recording sites in these two patients is shown in Figure 4. The largest difference between atrial fibrillation intervals at two adjacent sites was 22 ms in the patient with paroxysmal arrhythmia and 7 ms in the control patient. Reliable atrial signals were recorded at 247 sites in the patients with paroxysmal atrial fibrillation and at 118 sites in control patients. The mean atrial fibrillation interval was 152 ± 3 ms in the test group and 176 ± 8.1 ms

Figure 4. Spatial distribution of the differences in atrial fibrillation intervals at 37 and 32 sites, respectively, recorded simultaneously in the same patients as in Figure 3. Note that the bottom of the grid depicts 160 ms in the control patient (**upper panel**) and 120 ms in the patient with paroxysmal atrial fibrillation (**lower panel**).

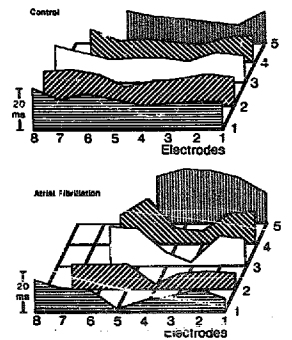

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Table 1. Summary of Recording Sites, Mean Atrial Fibrillation Interval and Variance in All Patients From Both Groups

	AF	Control	p Value
Patients (no.)	10	6	—
Recording sites (no.)	247	118	—
AF interval (ms)	152 ± 3	176 ± 8.1	<0.05
Variance (ms^2)	31.2	11.5	<0.001

Values are mean value ± SEM; AF = atrial fibrillation.

in the control group (Table 1). The difference of 24 ms in mean atrial fibrillation intervals between the two groups was statistically significant ($p < 0.05$).

To assess dispersion in atrial fibrillation intervals, the variance was calculated at all recording sites in both groups. In the patients with paroxysmal atrial fibrillation, the variance was 31.2 versus 11.5 ms^2 in the control group ($p < 0.001$) (Table 1). If we selected a subgroup of four patients with predominant sinus rhythm from the test group, these values were 29.2 versus 11.5 ms^2, respectively ($p < 0.005$). These observations do not prove, but they suggest, that increased dispersion in refractoriness is associated with the induction of atrial fibrillation rather than the consequence of this arrhythmia.

Discussion

The main findings of this study are 1) the mean atrial fibrillation interval was shorter in patients with recurrent paroxysmal atrial fibrillation than in control patients, and 2) patients with recurrent paroxysmal atrial fibrillation had three times greater dispersion in atrial fibrillation intervals than did control patients (Table 1).

Previous studies. *In previous experiments (10) in canine* hearts, we showed that during fibrillation cells are reexcited as soon as they have recovered their excitability and that fibrillation intervals can be regarded as an index of the shortest possible refractory period. In another experimental study, Lammers et al. (5) found a very good correlation ($r = 0.96$) between the local atrial refractory period determined with the extrastimulus technique and the atrial fibrillation interval at the same sites. The same high correlation was found between these two measurements in two patients (four sites in two patients each), although the number of sites at which refractory periods were measured was, for obvious reasons, very small.

Atrial fibrillation interval as an index of refractoriness. We used atrial fibrillation intervals to measure local atrial refractoriness simultaneously at multiple sites in patients with paroxysmal atrial fibrillation and patients without this arrhythmia. We found a significantly shorter atrial fibrillation interval (that is, index of atrial refractoriness) in the group with the paroxysmal arrhythmia (152 ± 3 vs. 176 ± 8.1 ms). A short effective refractory period has been found in some groups of patients with paroxysmal atrial arrhythmias (11,12).

Wavelength has been used as an index for susceptibility to reentrant arrhythmias in animal experiments (13,14). When the wavelength of a premature impulse is short, as a result of depressed conduction or shortened refractoriness, or both, small areas of conduction block may be sufficient to set up reentrant circuits. Because a critical number of wandering wavelets is required for perpetuation of atrial fibrillation, a shorter wavelength during fibrillation increases the average number of wavelets and, as a consequence, the stability of fibrillation (2). In animal experiments atrial fibrillation and intraatrial reentry can easily be induced in combination with vagal stimulation (14) or administration of acetylcholine (2,15,16). The fibrillatory action of parasympathetic transmitters is based on overall shortening of the refractory period (15). Also, in human patients, paroxysms of atrial fibrillation may be related to a high parasympathetic tone (17).

Initiation of reentry and unidirectional block. Heterogeneity of structural and electrophysiologic properties is thought to play a major role in the initiation of reentry because of the increased likelihood of unidirectional block of premature impulses (3,18–20). The significance of the dispersion of refractory periods necessary for the occurrence of unidirectional block has been emphasized in several studies (21–25). Alessi et al. (24) reported a dispersion of refractoriness of 40 ms in the right atrium of the dog, whereas Zipes et al. (26) found differences in refractory periods of 25 to 110 ms between seven locations in the canine right and left atria. Allessie et al. (3) reported differences on the order of 30 ms between the shortest and longest refractory periods in the isolated left atrium of the rabbit. In the same study (3), they found that when premature stimuli were delivered at the border of two areas with different refractory periods, a *dispersion between adjacent areas of 11 to 16 ms is sufficient* to create unidirectional block of a properly timed premature impulse.

In this study, we found a significant increase in dispersion of the atrial fibrillation intervals, which amounted to a threefold increase if expressed as variance (Table 1). Such an increase does not necessarily imply that chances for the occurrence of unidirectional block have also increased. From Figure 4 (lower panel) we can appreciate, however, that the increase in dispersion of atrial fibrillation intervals is not homogeneous over the entire grid, but rather localized. Thus, there is large dispersion between sites 5 and 6 in row 1, between sites 4 and 5 in row 2, especially between sites 2 and 3 in row 3 and between the complete rows 4 and 5. The maximal dispersion between adjacent sites in control patients was about 7 ms, whereas this figure could be as high as 22 ms in patients with recurrent atrial fibrillation. Such a difference between adjacent sites during atrial fibrillation would be 37 ms at basic cycle length if the relation between atrial fibrillation and refractory period from Figure 2 is used as an estimate. This difference between adjacent sites is much more than the 11 to 16 ms known to be needed for unidirectional block of premature pulses in rabbit atria (3).

The mechanism responsible for the increased dispersion of refractoriness might be the nonuniform state of the diseased atrial cells (27).

Conclusions. Our data cannot exclude that the shortening and increased dispersion in atrial fibrillation intervals in the test group are the corollary of atrial fibrillation instead of the cause of induction. More experiments are needed to settle this issue. However, the fact that none of our patients with paroxysmal atrial fibrillation had aberrant atrial dimensions suggests that the overall shortening of the refractory period and an increased dispersion in refractoriness are associated with the genesis of atrial fibrillation at least in this study group.

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